

## CLINICAL REPORT

# Long-term Follow-up of *In situ* Extramammary Paget's Disease in Asian Skin Types IV/V Treated with Photodynamic Therapy

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**Photodynamic therapy is a potentially advantageous treatment for non-melanoma skin cancers. We evaluated the clinical response, recurrence and adverse events of photodynamic therapy for *in situ* extramammary Paget's disease in 14 male and 3 female Chinese patients with 21 lesions. Topical 20% 5-aminolevulinic acid was applied for 6 h. Each lesion was irradiated with 633 nm red light three times, 1 week apart, at a total dose of 339 J/cm<sup>2</sup>, followed by three assessments at 6, 12 and 24 months. Overall complete response (CR) rates were 52.4%, 42.9%, and 33.3% at 6, 12 and 24 months, respectively. The CR rate was significantly higher in scrotal lesions (66.6%) than in non-scrotal lesions (8.3%). The overall recurrence rate was 50%. The highest CR rate was for the lesions <4 cm in diameter (62.5%), followed by those 4–8 cm (33.3%) and >8 cm (0%). Most adverse events were well tolerated. In conclusion, photodynamic therapy for extramammary Paget's disease is not recommended as the first option except for scrotal cases or lesions <4 cm in diameter. Key words: Paget's disease; extramammary; photochemotherapy; aminolaevulinic acid.**

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Extramammary Paget's disease (EMPD) is an uncommon intraepithelial neoplasia localized in apocrine sweat gland-rich regions, such as the scrotum, axillary areas, perianal areas and the vulva. It usually affects patients between 65 and 70 years of age, especially postmenopausal Caucasian females (1–3). However, in the Chinese population, EMPD seems to affect more males than females, and the scrotum and perianal areas are the most commonly involved sites (4). Clinically, onset of the disease is insidious, with bleeding, oedema or subjective symptoms (itch, burning or pain). EMPD tends to have a good prognosis because the spread of atypical cells is usually limited to the epidermis.

Adequate local surgical excision is currently the standard treatment for *in situ* or invasive EMPD. However, excision is insufficient to achieve complete remission, and the frequency of recurrence ranges from 15% to 44%. Recurrence is associated with invasion of Paget's cells in the epidermis that largely exceeds the visible margin of the lesions (5–7). Hendi et al. demonstrated that a low recurrence rate could be achieved by Mohs micrographic surgery, and a 4-cm margin was recommended for cases where such surgery is not available (7). Several non-invasive modalities, such as X-ray radiotherapy and systemic plus local chemotherapy, are proposed for inoperable lesions or as a combined treatment with surgical excision (8–10). Recently, imiquimod, a topical imidazoquinoline immunomodulator, has been frequently reported as a treatment for primary or relapsing EMPD (11–13). However, none of these therapies prevent recurrence and achieve a high cure rate. Multicentric invasion and ill-defined tumour margins are still the most important risk factors.

Photodynamic therapy with 5-aminolevulinic acid (ALA) is a potentially advantageous treatment modality for non-melanoma skin cancers, such as actinic keratosis, basal cell carcinoma and Bowen's disease. This alternative drug-based approach was first described by Kennedy et al. (14). ALA is preferentially taken up and converted into protoporphyrin IX (PpIX) by neoplastic cells. Pp IX activated by 630-nm laser selectively destroys tumour cells, while sparing healthy tissue and cells. Thus, this PDT using a large-field light source is expected to solve the problem of high recurrence rate, because the light-emitting diodes (LED) may provide an extensive illumination area such as to kill a large number of invisible atypical cells in disease-free normal skin. One ALA-PDT study using LED achieved a complete response (CR) rate of only 50% after 6 months (15). Methyl aminolevulinic acid (MAL), a novel photosensitizer precursor, has shown deeper tumour penetration and less adverse effects than ALA, due to its enhanced lipophilicity (16, 17). However, one MAL-PDT study on 7 patients still failed to achieve favourable results, with clinical and histological cure rates of only 57% and 21%, respectively (18). These studies suggest that the key factor for the high recurrence rate is not the treatment

parameters of topical PDT, but rather the characteristics of EMPD. Thus, the recurrence rate is lower for scrotal EMPD (0%) than for non-scrotal EMPD (50%) (15). One combination therapy with the topical PDT and CO<sub>2</sub> laser achieved a CR rate of 100% (2/2) in scrotal EMPD at 12 months (19). To our knowledge, there have been no clinical studies which are addressed on the association between tumour location and therapeutic response to EMPD treated with ALA-PDT. Therefore we conducted a prospective observational study to evaluate the clinical response, recurrence, adverse events and cosmetic outcome of ALA-PDT for *in situ* EMPD, and we investigated possible prognostic factors, such as tumour location, size and thickness.

## MATERIALS AND METHODS

This was a prospective non-comparative observational study addressing the therapeutic response and side-effects of ALA-PDT treatment for *in situ* EMPD. The study was approved by the ethics committee of the Fourth Military Medical University.

Patients with EMPD were recruited from the dermatology clinic of Xijing Hospital, Xi'an (China), between September 2004 and October 2008. Patients gave written informed consent before study entry. EMPD was clinically diagnosed by two physicians and subsequently confirmed by an incision biopsy taken from the thickest part of the lesions. Patients who were aged > 18 years, histologically verified to have *in situ* EMPD, and suitable for PDT were included in the study. Exclusion criteria were the following: metastasis or invasive EMPD, tumour thickness of > 2 mm, poor general health, poor compliance, pregnancy, breastfeeding, or other treatments within the previous 6 months.

Crusts were removed by curette to facilitate access by the photosensitizer. Topical 20% (w/w) ALA (Biosynth, AG, Staad, Switzerland) in an oil-in-water emulsion was applied to lesions with a 20-mm margin of disease-free skin, which were then sealed with thin plastic wrap and covered with non-adhesive light-shielding dressings for approximately 6 h. After removal of excess cream using saline buffer, the lesion with at least 50 mm normal margin was irradiated with a red light (wavelength: 633 nm; intensity: 126 mW/cm<sup>2</sup>) from a LED lamp (Omnilux, Altrincham, Cheshire, UK). Each lesion was irradiated for 15 min for a total light dose of 113 J/cm<sup>2</sup>. To mitigate any hyperthermic effects or burning sensation, the treatment was divided into two 7.5-min sessions separated by 30 min. The light source was calibrated before illumination using a MACAM SR-9910 spectroradiometer (Macam Photometrics, UK). The above procedures were conducted three times, each one week apart, for a cumulative dose of 339 J/cm<sup>2</sup>.

Six months after final treatment, the clinical response was evaluated as complete or incomplete by clinical inspection by the same investigator. "Complete response" was defined as disappearance of the lesion. Lesions with incomplete response received an alternative treatment of surgical excision, cryotherapy or CO<sub>2</sub> laser therapy. The investigator-assessed cosmetic outcomes were evaluated by a blinded observer. The patient outcome was graded as excellent (no hypertrophic scarring, atrophy nor induration; no redness; no difference in pigmentation compared with neighbouring skin); good (no hypertrophic scarring, atrophy nor induration, but slight redness or pigmentation); fair (slight to moderate hypertrophic scarring, atrophy or induration; moderate redness or pigmentation) or poor (extensive hypertrophic scarring, atrophy and induration,

or serious redness or obvious pigmentation). Each patient and/or one family member completed an additional questionnaire for self-evaluation that used these four criteria. The evaluations were repeated at 12 and 24 months.

Any adverse events were documented during cream application or during/after illumination at each visit. Pain was scored by visual analogue scale (VAS) assay, ranging from 0 (no pain) to 10 (extreme pain) (20). Other events, such as unfavourable or unintended signs, or symptoms reported spontaneously by the patients or elicited after non-leading questioning were noted, together with their severity, duration and requirement of additional therapy. Local and systemic phototoxic reactions were reported up to 3 months and graded by the National Cancer Institute Common Toxicity Criteria (21).

Histological changes were reported by three dermatopathologists at the People's Liberation Army Institute of Dermatology, Xijing Hospital. The skin samples were taken by incision biopsy under local anaesthesia (10 mg/ml lidocaine), fixed in 10% formaldehyde, embedded in paraffin and stained by haematoxylin and eosin. This was repeated at 6, 12 and 24 months. All biopsies were taken from the previous treated area. Tumour depth was calculated from the stratum corneum to the lowest boundary of the tumour on pathological photomicroscopic images (Nikon 90i, Tokyo, Japan), and a 100- $\mu$ m scale was added as reference. Histological changes, including fibrosis, inflammatory cells and lentigo-like features (hyperplasia, basal layer pigmentation, and melanophages in the papillary dermis), were described. Lesions that presented clinical remission but histological remnants of tumour cells were regarded as "treatment failure" (partial disappearance or recurrence). Only lesions confirmed as CR by three clinical and histological examinations at 6, 12 and 24 months were regarded as "treatment success" (CR of tumour).

Statistically, data were reported as numbers and/or percentages. Pearson  $\chi^2$  test was used for comparing CR rates. A *p*-value of <0.05 or <0.01 was considered statistically significant. Statistical analysis was carried out using the SPSS 10.0 software application.

## RESULTS

Sixteen patients with 21 lesions, who had previously untreated biopsy-proven EMPD *in situ*, were enrolled. All had type IV/V skin. The patients' mean age was 68.2 years, and 85.7% were male. Relevant clinical details, such as lesion number, location, size (largest diameter), course and tumour thickness, are summarized in Table I. One perianal EMPD was associated with underlying colorectal carcinoma.

For all 21 lesions undergoing ALA-PDT therapy, CR was confirmed in 11 (52.4%) lesions at 6 months, 9 lesions (42.9%) at 12 months, and 7 (33.3%) lesions at 24 months, based on clinical and/or histological examinations. No significant differences in CR rates were seen among the three visits ( $\chi^2 = 1.5556, p > 0.05$ ). Seven lesions (2 axillary, 4 perianal, 1 vulval) showed partial response after three treatments. Seven lesions recurred during 24 months. The 14 lesions with incomplete response were treated with alternative therapies.

The CR rate significantly was correlated with tumour location and size. At 24 months (Table II), the scrotal lesions showed greater response to PDT (66.6% (6/9)) than the axillary (20% (1/5)), perianal (0% (0/5)), and

Table I. Characteristics of patients and lesions with in situ extramammary Paget's disease

Characteristics	
Number of patients	16
Sex (M/F)	14/2
Mean age (range), years	68.2 (54–83)
Number of lesions	21
Location of lesion, <i>n</i> (%)	
Scrotum	9 (42.9)
Axillary area	5 (23.8)
Perianal area	5 (23.8)
Vulval area	2 (9.5)
Mean course of disease (range), months	32.5 (2–120)
Mean size of lesions (range), cm	3.7 (1–12)
Mean tumour depth (range), mm	0.44 (0.2–1.4)
Underlying malignancy, <i>n</i>	1

vulval lesions (0% (0/2)). A significant difference was observed between scrotal and non-scrotal EMPD (66.6 vs. 8.3%;  $\chi^2=7.87$ ,  $p<0.01$ ). No obvious difference was observed in the mean size of tumour between the two groups (6.2 vs. 5.5 cm diameter). Similar results were seen at 6 and 12 months, although the difference observed was not significant, due to the small sample sizes. At 6 months (Table III), the CR rate was 75% (6/8) for diameters < 4 cm, 66.7% (4/6) for diameters 4–8 cm, and 14.3% (1/7) for diameters > 8 cm, regardless of tumour location and course. No significant difference was observed between < 4 cm and 4–8 cm, due to the small sample size. Similar results were seen at 12 and 24 months, and there was significant difference in CR rate at 24 months between < 4 cm (75% (6/8)) and the other two groups (15.4% (2/13)) ( $\chi^2=7.4634$ ,  $p<0.01$ ). These data suggest that the therapeutic response was associated with tumour size. Moreover, as shown in Table III, there were no significant differences in CR rate among tumour depth groups.

After final treatment, 7 lesions showed partial response, 14 lesions showed clinically CR. At 6 months, 3 of 14 lesions were histologically verified to have recurred. The other 2 and 2 lesions successively recurred 6 and 12 months later. The overall recurrence rate was 50% (7/14), including 2 scrotal, 2 axillary, 1 perianal and 1 vulval lesion. Tumour recurrence seemed to correlate

with lesion size. At 6 months, the < 4 cm, 4–8 cm, and > 8 cm groups showed recurrence rates of 0% (0/5), 25% (1/4), and 40% (2/5). Similar results were observed at 12 and 24 months.

Seven of 7 (100%) patients with CR were satisfied with the cosmetic outcome. Interestingly, 5 of 14 (35.7%) incomplete response lesions were rated as good or excellent cosmetic outcomes; the remaining 9 lesions were rated as poor cosmetic outcomes for atrophy ( $n=2$ ), induration ( $n=1$ ), depigmentation ( $n=4$ ) and redness ( $n=2$ ). We observed no other side-effects, such as hypertrophic scarring or pigmentation (Fig. 1). Moreover, anatomical function was well preserved in all patients.

There were no serious adverse events or deaths. All of the patients experienced specific skin reactions to the PDT during and/or after the illumination. Mild to moderate erythema and oedema developed on all of the treated areas. Erosion and crusting occurred after 24 h and disappeared within 14 days. Slight or mild discomfort, including itching, hot feeling and/or burning sensation, was reported by two-thirds of patients during irradiation. This discomfort was well tolerated in most cases. However, 12 of 16 patients could not endure the acute pain caused by the LED irradiation and were given anaesthesia. VAS scoring showed that the mean  $\pm$  SD of pain during PDT in 16 patients was  $5.4 \pm 1.3$ , ranging from 2 to 10. Pain sensitivity in descending order of severity was perianal (mean pain score of 9.1), vulval (6.5), axillary (4.5) and scrotal (3.2). From the results above, the lesions from skin mucous membranes or the interface seemed to be sensitive to pain. No local or systemic photosensitivity reaction was reported for up to 3 months.

Histological changes were similar at 6, 12 and 24 months, such as epidermal reconstitution, dermal fibroblasts proliferation and tumour disappearance (Fig. 1). The number of melanocytes was definitely decreased at the basal epidermal layer of skin compared with neighbouring normal skin, which contributed to clinically local slight depigmentation. Furthermore, some eosinophils and histiocytes were seen in the papillary dermis. Capillary vessels with dilatation and proliferation were obvious and frequent. The changes disappeared gradually after 6 or 12 months.

Table II. Complete response rate vs. time according to location of in situ extramammary Paget's disease

	Complete response rate			Mean tumour depth $\pm$ SD (mm)
	6 months	12 months	24 months	
Scrotal	77.8% (7/9)	66.6% (6/9)	66.6% (6/9)	0.34 $\pm$ 0.16
Non-scrotal	33.3% (4/12)	25.0% (3/12)	8.3% (1/12)	0.45 $\pm$ 0.12
Axillary	60.0% (2/5)	40.0% (2/5)	20.0% (1/5)	0.33 $\pm$ 0.13
Perianal	40.0% (2/5)	20.0% (1/5)	0.0% (0/5)	0.41 $\pm$ 0.17
Vulval	0.0% (0/2)	0.0% (0/2)	0.0% (0/2)	0.65 $\pm$ 0.41
Total	52.4% (11/21)	42.9% (9/21)	33.3% (7/21)	

SD: standard deviation.

Table III. Complete response rate and lesion course according to tumour size and depth

Lesion	Complete response rate			Mean course (months)
	6 months	12 months	24 months	
< 4 cm	75.0% (6/8)	75.0% (6/8)	62.5% (5/8)	28.3
4–8 cm	66.7% (4/6)	50.0% (3/6)	33.3% (2/6)	48.7
> 8 cm	14.3% (1/7)	0.0% (0/7)	0.0% (0/7)	36.6
Tumour depth				
< 0.4 mm	50.0% (6/12)	41.7% (5/12)	33.3% (4/12)	36.2
0.4–0.8 mm	50.0% (3/6)	33.3% (2/6)	33.3% (2/6)	24.1
> 0.8 mm	66.7% (2/3)	66.6% (2/3)	33.3% (1/3)	54.9



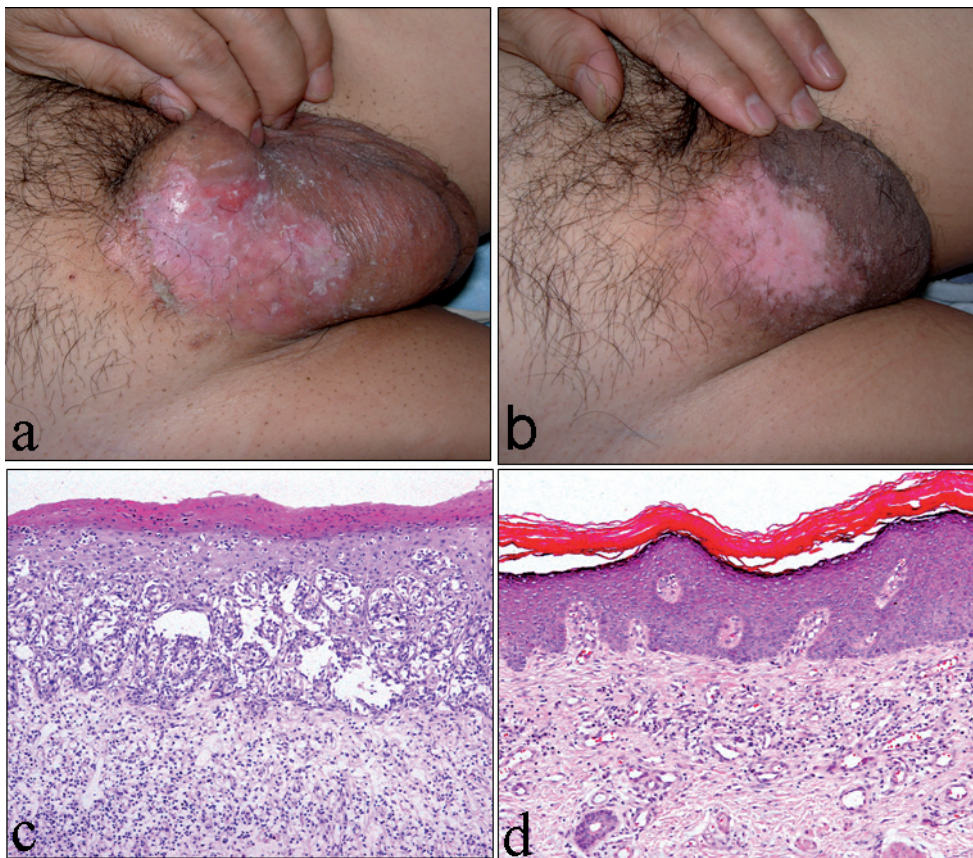


Fig. 1. Clinical changes of *in situ* extramammary Paget's disease on the scrotum before (a) and 6 months after (b) photodynamic therapy. Histology after treatment (d) shows disappearance of Paget's cells (abundant basophilic or amphophilic cells, finely granular cytoplasm; the cell tends to stand out in contrast to the surrounding epithelial cells), reconstituted epidermis with decreased melanocytes, slight fibrosis, and capillary vessels with greater dilatation than before the treatment (c).

## DISCUSSION

This long-term observational study demonstrated that ALA-PDT had limited effectiveness in treating *in situ* EMPD. The overall long-term CR rate was only 33.3%, and the recurrence rate reached 50%. Partial response was shown in 33.3% of lesions. The CR rate was lower in this study than in two previous ALA-PDT studies on primary and recurrent vulval EMPD (50% and 57.1%) (15, 18). This difference is possibly related to skin type, with the Asian skin type (IV/V) being more resistant to light penetration than the Caucasian skin type (II/III) (22). Another possibility is the parameters or enrolment criteria. The LED system (Omnilux, UK) releases light of lower intensity ( $126 \text{ mW/cm}^2$ ) than that of other laser and incoherent light sources, which potentially yielded the low CR rate. On the other hand, the LED's larger field of illumination was expected to make the LED superior at eradicating some clinically invisible cells in disease-free skin. Yet, the recurrence rate reached 21.4% in the early phase. At long-term follow-up, it had risen to 50%, which was higher than the previously reported 37.5% (15). To date, no multi-centre and/or multi-ethnic study has been conducted. Nevertheless, PDT is not recommended as a first option for most *in situ* EMPD.

This study demonstrated that scrotal EMPD is more responsive to PDT than non-scrotal cases. The peria-

anal and vulval lesions appeared to be more resistant to the therapy. It is difficult for topical ALA emulsion to completely cover the whole lesion in these areas. It is difficult for topical ALA emulsion to completely cover the whole lesion in these areas. Especially, recesses or anal canal in the perianal and vulval lesions would be potential tumour recurrence sites. In contrast, the scrotum is relatively flat, which facilitates complete access by the ALA emulsion. Moreover, perianal, axillary, and vulval areas are densely distributed with apocrine sweat glands and dermal appendages where tumour cells are thought to originate from intraepidermal gland duct cells (23). Some atypical cells invade along the ducts up to the recommended tumour response depth of 3 mm (24). In contrast, dermal appendages are relatively sparse in the scrotum; thus, there is less chance of deep invasion, and eventually the recurrence rate should be lower in scrotal lesions than the other lesions. In this report, the  $> 4 \text{ cm}$  lesions showed unfavourable CR, due to dense infiltration by Paget's cells and much more adnexal involvement, followed by disproportionate ALA-induced PpIX accumulation in apocrine glands, which resulted in photodynamic oxygen depletion and tumour recurrence (25). Tumour thickness seems not to be key factor in the therapeutic response. No obvious correlation was observed between CR rate and tumour thickness. The pathological features of EMPD, such as the presence of intraepidermal Paget's cells and sub-

clinical intraepithelial diffusion, determines that the tumour thickness of EMPD is usually less than 3 mm which has been recommended as the tumour response depth (24). Taken together, these data indicate that the therapeutic response significantly correlates with tumour location or size, but not with tumour thickness. Topical PDT might be recommended as a first option for *in situ* scrotal EMPD or lesions <4 cm in diameter.

Functional preservation and cosmetic outcome for ALA-PDT were superior to those seen for invasive therapies such as surgery, radiation and curettage. All of the patients with CR were satisfied with the cosmetic outcome. In a retrospective review of five female patients with anogenital, groin and axillary EMPD treated with ALA-PDT, although only 8 of 16 (50%) lesions achieved CR, and the recurrence rate reached 37.5% after 6 months, functional preservation and cosmetic outcomes were accepted by all patients (15). Thus, functional preservation is necessary for the elderly with poor health or those with high requirements as to the quality of life, such as sexual activities.

EMPD is a rare cutaneous tumour, and published studies are limited to small case series of patients (15, 18, 26). The treatment parameters largely varied with respect to illumination dose, concentration of photosensitizer precursor, and wavelength of light source. Thus, a multi-centre and/or multi-ethnic study is required for analysing the effectiveness of PDT in the future. In conclusion, this study suggests that PDT has the advantages of being non-invasive and well-tolerated, but the disadvantages of having a low clearance rate and high recurrence rate. However, PDT may benefit patients who have poor surgical conditions or high requirements for cosmesis and quality of life. We emphasize that it is not recommended as the first treatment option for most patients, except for scrotal cases or lesions <4 cm in diameter.

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*The authors declare no conflicts of interest.*

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